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THE EFFECT OF CARBOPLATIN CHEMOTHERAPY REGULATION ON HEARING FUNCTIONS IN PATIENTS OF NASOPHARYNGEAL CARCINOMA

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Abstract

Introduction: The incidence of hearing loss after treatment with carboplatin-based chemotherapy in nasopharyngeal carcinoma (NPC) patients were evaluated, and relationships of loss with host factors, treatment-related factors were investigated.

Objective: To evaluate the effect of giving a carboplatin chemotherapy regimen for 6 times chemotherapy (serial chemotherapy) on hearing function in patients with nasopharyngeal carcinoma. The incidence of hearing loss after treatment with carboplatin-based chemotherapy in nasopharyngeal carcinoma (NPC) patients were evaluated, and relationships of loss with host factors, treatment-related factors were investigated.

Method: Thirty NPC patients were treated with carboplatin chemotherapy from 2015 to 2017 were analyzed. Pure tone audiometry and Distortion Product of Otoacoustic emission (DPOAE) were performed during the follow-up period, with a median time of 36 months, ranging from 24 to 36 months. Correlation of SNHL at frequencies (pure tone average, 0.5-8 kHz) with a series of factors was analyzed.

Results: Among 30 participant (60 ears), using the Wilcoxon test, the mean threshold after series III was significant (p=0,000) and the mean of after series VI and significant (p= 0,000). The relationship between DPOAE results and pure tone audiometry was also carried out in the early stages of series III. Kaplan Meier's survival analysis improvement from post-III series (6 weeks) of participants who survived as many as 23 participants (76.67%) and in the post-chemotherapy evaluation of VI series (15 weeks) participants who survived as many as 8 participants. Bivariate statistical analysis using the Spearman non-parametric correlation test, there was a significant relationship between the mean dose and the decrease in the hearing threshold. p=0.00 (<0.01).

Conclusion: For NPC patients treated with carboplatin chemotherapy, There was an effect on the hearing function of the administration of carboplatin chemotherapy regimen for 6 series chemotherapy in patients with nasopharyngeal carcinoma.

Article Info

Keywords:

Nasopharyngeal carcinoma, hearing loss, carboplatin

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1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) has been considered as one of the theater neoplasms globally. It is relatively frequent in some regions, including parts of South-Eastern Asia and a number of provinces in South-Eastern China From various reports mentioned that the malignancy in the neck head area is still a major health problem in the world, with an estimated 500,000 new cases each year. Among the various malignancies in the head area of the neck most often found in Indonesia are nasopharyngeal carcinoma with an incidence of around 4.7-30 cases per 100,000 inhabitants [1-5].

Platinum-based chemotherapy consisting of cisplatin, carboplatin, and oxaliplatin, satraplatin, and transplatin have been used extensively in clinics since thirty years ago in the treatment of malignant head-neck tumors so that the side effects of using chemotherapy agents also need serious attention, one of them being ototoxic. Ototoxicity of platinum group chemotherapy drugs tends to cause sensorineural hearing loss that persists at high frequencies. Sensorineural deficits will increase as the drug dose accumulates. Carboplatin is the second generation platinum-based with nephrotoxic effects and ototoxic cochlear which tend to be lower than cisplatin. In various studies, it was found that the incidence of cisplatin ototoxicity was high enough that it had begun to be abandoned. However, the use of high doses of carboplatin or long-term accumulations of accumulation can occur in the inner ear ototoxicity. The pathogenesis of carboplatin ototoxicity is similar to that of cisplatin. Like cisplatin, carboplatin causes damage to Corti's organs. However, the target of damage caused by carboplatin in the initial phase is thought to begin from the hair cells continuing to the outer hair cells while the target damage caused by cisplatin begins in the outer hair cells. Outer hair cell damage has been observed in the use of high-dose carboplatin and long-term use [3-7].

Carboplatin is a second generation analog platinum that has been used extensively in chemotherapy. The chemical formula structure is diamine [1,1-cyclobutanedicarboxylato (2 -) - O, O '], (SP-4-2). Carboplatin is a second generation platinum analog of cisplatin consisting of central platinum atoms in the same plane as two groups of ammonia and chloride or 1,1-cyclobutanedicarboxylate with a ligand in the cis position. Carboplatin is considered to have a nephrotoxic and ototoxic effect at relatively lower therapeutic doses than cisplatin so that it is more widely used today as a platinum substitute for cisplatin. Ligands found in the form of carboplatin ring structures tend to be stable compared to the two chloride arms found in the cisplatin structure. This difference causes the molecular stability of carboplatin with a decrease in the toxic effects of the drug, including ototoxicity. The exact mechanism of carboplatin cytotoxicity is not clearly known. Carboplatin, like cisplatin, can induce DNA chains, although it requires 10 times higher drug concentrations and 7.5 times longer than cisplatin. Carboplatin becomes hydrolyzed, similar to cisplatin but a hundred times slower [8-13].

Large doses of carboplatin are often used to improve the antitumor response. Ototoxicity of carboplatin is expressed as damage to hair cells in the cochlea. Carboplatin in the form of crystalline powder with the molecular formula C6H12N2O4Pt and molecular weight around 371.25. Carboplatin is mixed with a water solvent of about 14 mg/mL, with Ph of 1% solution around 5-7. Generally, carboplatin dissolves in ethanol, acetone, and dimethylacetamide. Carboplatin is chemically less active than cisplatin; its toxic effects are considered lower in the ears, kidneys, and central nervous system. Thus the reactivity is lower in concentrations that are quite large compared to the cisplatin needed to fight malignant tumors; thus the dose needed will be even greater. It is estimated that the dose needed is around 8-45 times compared to cisplatin [14-19].

Carboplatin is also known to damage the kidneys (nephrotoxic) and the inner ear (ototoxicity). 30-32 Long-term exposure of alkaline agents can cause 10 to 15 times increased resistance. Research shows a response by causing the synthesis of glutathione and metallothionein. Metallothionein is a protein that binds heavy metals and achieves increased levels of metals in the blood [19-22].

Carboplatin, as well as predominant cisplatin, affects the DNA chain path compared to its DNA protein. This effect is not specific to the cell cycle. Activation of carboplatin tends to be slower because its solubility is longer than cisplatin although its mechanism of action is similar to that of double chain DNA, causing similar biological lesions, the difference being in the potentiation of lower carboplatin due to differences in solubility. In patients with a creatinine clearance of about 60 mL/minute or more, plasma levels of carboplatin in a biphasic method occur after 30 minutes with intravenous infusion of 300 mg/m2 to 500 mg/m2 carboplatin [23-28].

The half-life of plasma (alpha) is 1.1 to 2 hours (n=6), and the half-life after the distribution period (beta) is 2.6 to 5.9 hours (n=6). Total body clearance, close to distribution volume and the average time is 4.4 L / hour, 16 L and 3.5 hours. The Cmax values and areas below plasma concentrations of the time curves from 0 to infinity (AUC) increase linearly according to the dose, although the increase tends to exceed proportional doses. Carboplatin thus inhibits linear pharmacokinetics when it exceeds the studied dose range (300 mg/m2–500 mg/m2) [19, 20].

Studies in several experiments on animals have shown that the therapeutic dose of carboplatin can selectively cause damage to hair cells in the cochlea and type I ganglion neurons without damaging the cochlear outer hair cells. Selective damage from hair cells in the cochlea does not cause a potential cochlear microphone effect and DPOAE However, carboplatin in high doses or long-term accumulated doses can damage the inner hair cells as well as the outer cochlear hair cells causing a decrease in the amplitude of the cochlear microphonics in DPOAE [29-34].

Carboplatin does not bind to plasma proteins. There is no significant free protein, as is the presence of other platinum groups in the plasma. However, platinum from carboplatin to irreversible is bound to plasma proteins and eliminated slowly with a half-life of at least 5 days. The major pathway for eliminating carboplatin is renal excretion [1-5, 22-24].

Patients with creatinine clearance close to 60 mL/minute or excretion of 65% of the urine dose in 12 hours and 71% of the dose within 24 hours. All platinum in the urine 24 hours out as carboplatin. The remaining only about 3% to 5% is given platinum and then excreted in urine between 24 and 96 hours. There are no data yet to explain whether biliary excretion also occurs. In patients with creatinine clearance below 60 mL/minute with total body clearance and renal clearance of carboplatin decreases with decreasing creatinine clearance [30, 31].

Carboplatin as a single dose of therapy (injection of carboplatin fluid) should be given at a dose of 360 mg /m2 IV over 15-60 minutes at 1 day every 4 weeks. The intermittent dose of carboplatin should not be repeated until a minimum neutrophil count of 2,000 and 100,000 platelets. Patients with creatinine clearance below 60 mL/minute risk bone-marrow suppression including severe leukopenia, neutropenia, and thrombocytopenia [34-36].

2. MATERIAL AND METHODS

Based on the medical record in RSUP. Dr. Moh. Hoesin Palembang in 2015 to 2017, it found a total number of patients undergoing chemotherapy 270 patients with head and neck regional carcinoma who were treated in the Department of Surgery, Department of Internal Medicine, Department of Children and ENT-KL Department. Of the 270 patients who underwent chemotherapy, as many as 129 patients used the carboplatin chemotherapy regimen. Data obtained from the Oncology Subdivision of the ENT-KL Department of RSUP. Dr. Moh Hoesin Palembang from 2015 to 2017 found 129 patients with Nasopharyngeal carcinoma undergoing chemotherapy with a carboplatin regimen. This study used a prospective observational method to determine ototoxic events in the form of decreased hearing function in patients with nasopharyngeal carcinoma who underwent chemotherapy with carboplatin in 6 series (1 cycle) chemotherapy. This research has been carried out from June 2015 until February 2017. The number of samples that met the acceptance criteria and participated in this study were 30 participants from 25 minimum participants needed.

3. RESULT

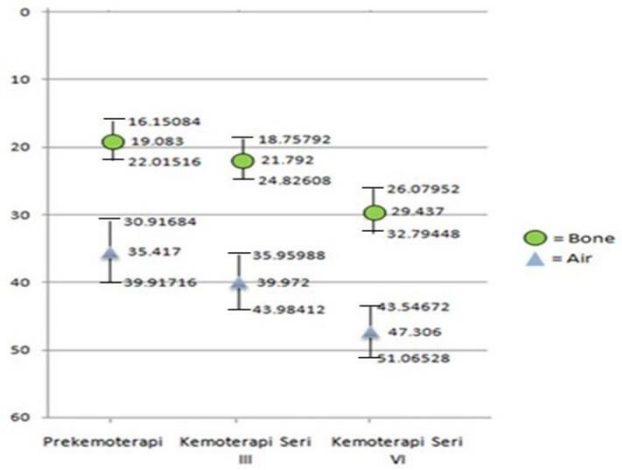
3.1 Characteristics of decreasing hearing functions based on evaluation of pure tone audiometry.

The study was done in 30 participants with the number (n) of each ear obtained in a total of 60 years. Characteristics based on type and degree of hearing loss in preliminary pure-tone audiometry screening performed before chemotherapy, obtained ears with normal hearing of 36 ears (60%), mild conductive hearing loss as much as 8 ears (13.3%), moderate conductive hearing loss as much as 12 ears (20%), heavy conductive hearing loss as much as 2 ears (3.33%), mild sensorineural hearing loss of 1 ear (1.7%), moderate sensorineural hearing loss of 1 ear (1.7%).

In the post III series chemotherapy evaluation it was found that 27 ears (45%) with normal hearing, 5 ear mild conductive hearing (8.30%), 7 (11.67%) moderate conductive hearing, and 2 conductive hearing loss (3.30%). Sensorineural hearing loss has increased in number with 6 (10%) ears with mild sensorineural hearing loss and 5 (8.30%) ears with moderate sensorineural hearing loss. Conductive-sensorineural hearing loss obtained mild hearing loss of 4 (6.67%) ears and moderate mixed hearing loss as much as 4 (6.67%) ears. Audiometry evaluation after series VI chemotherapy found normal ears (16.67%) of ears, mild conductive hearing loss of 4 (6.67%) ears, moderate conductive hearing loss of 6 (10%) ears. Mild sensorineural hearing loss was obtained in 10 (16.67%) ears; the moderate sensorineural hearing loss was obtained 9 (15%) ears, severe sensorineural hearing loss was 3 (5%) ears. Mild hearing loss is obtained in 9 (15%) ears, and moderate hearing loss is 6 (10%) ears.

Based on the results of pure tone pre-chemotherapy audiometry evaluation, post series III chemotherapy and post-series VI chemotherapy, the mean changes in bone delivery threshold and airborne threshold, i.e. mean bone threshold (table 2), were found at 19.0833+11.585 after post-chemotherapy series the mean hearing threshold of bone is 21.7917+11.988. The conductive bone hearing in the post VI chemotherapy series showed a significant increase to 29.4375+13.271.

Graphic 1 Changes in Threshold of Air Channel and Bone Conduction based on Pure Tone Audiometry Results (n=60)



Analysis of changes in mean bone conduction threshold and air conduction was carried out by the Wilcoxon test (table 1), where a significant change in bone delivery threshold after series III (p=0.000) and mean change in bone delivery threshold after series VI was also significant (p=0.000). The mean change in air conductivity threshold after series III is significant (p=0.000) and the mean change in air conductivity threshold after series VI is also significant (p=0.000).

Table 1. Wilcoxon Test for Changes in the Average of Hearing Threshold of Air Delivery and Bone Delivery (n=60)

	Bone Conduction Threshold Mean + SD	Z	p	Air Conduction Treshold Mean + SD	Z	p
Pre-Kemo	19.08+11.54			35.41+17.63		
		-4.096	0.000		-3.944	0.000
Pasca Seri III	21.79+11.98			39.97+15.72		
		-5.576	0.000		-4.891	0.000
Pasca Seri VI	29.43+13.27			47.30+14.73		

Wilcoxon test is significant if p <0.005

In this study, the degree of ototoxicity was assessed by two criteria, namely the National Cancer Institute's NCI-CTCAE criteria—the Common Terminology Criteria for Adverse Events and the criteria for ASHA (1994). Both of these criteria are still widely used and are standard criteria in monitoring the ototoxic events of chemotherapy drugs and other drugs. The NCI-CTCAE Criteria (National Cancer Institute-Ototoxicity Grade Common Criteria for Adverse Events (NCI-CTCAE) in post III series chemotherapy evaluation, of the 30 participants studied (n=30) were considered more sensitive in detecting ototoxicity in the initial phase is divided into degrees I, II, and III ototoxic. Ototoxic grade I generally without complaint than usually decreases only occur unilaterally on two consecutive frequencies at high frequencies. Participants generally can still communicate well at the frequency of conversation but still an emotion. They are ototoxic degree II (26.67%) and grade III (6.67%). Participants generally began to complain of hearing loss (table 2).

The ASHA criteria (1994) are assessed bilaterally in both ears so that the initial and unilateral phases are usually not detected. However, many researchers conclude that this criterion is the most ideal for declaring an ototoxic diagnosis that occurs bilaterally. In this study, ototoxicity in post-series III occurred as much as 10%, and post-series VI occurred in 33.30%.

Table 2. Degrees of autotoxicity based on NCI-CTCAE Criteria (n=30)

Grading Ototoxicity	Chemo III		Chemo VI	
	n	%	n	%
Normal	23	76.67%	8	26.67%
Grade I	5	16.67%	12	40%
Grade II	2	6.67%	8	26.67%
Grade III	0	0.00%	2	6.67%

Table 3. Degrees of ototoxicity based on ASHA Criteria (n=30)

Ototoxicity Degree	After Chemotherapy series III		After Chemotherapy series VI	
	n	%	n	%
Normal	27	90.00%	20	66.67%
Ototoxicity	3	10.00%	10	33.30%

Table 4. Conformity Test of NCI-CTCAE Autotoxicity Criteria with ASHA Criteria (n=30)

	NCI series III		NCI seri VI	
	Normal	Ototoxic	Normal	Ototoxic
ASHA series III				
Normal	1	0		
Ototoxicity	0	1		
ASHA seri VI				
Normal			0	1
Ototoxicity			1	0
Kappa	1.00		-1.00	
Std Error	0.000		0.000	

3.2 Characteristics of decreasing hearing functions based on DPOAE evaluation

Tympanometry screening pre-chemotherapy was performed on 60 ear samples, and the results of type A tympanogram were 36 (60%) ears, As-type tympanogram as much as 2 (3.33%) ears, type B tympanogram 18 (30%) ears and type C tympanogram as many as 4 (6.60%) ears. Then 38 ear types A and As samples were monitored with DPOAE in post III and VI series. In post series III evaluation of 38 samples, there were 32 (53.3%) type A tympanogram results and As (a type of As-type tympanogram) 6 (10%) ears. In the post VI series evaluation, the results of type A tympanogram were 28 (46.67%) ears and As type as many as 10 (16.67%) ears.

Ototoxicity can also be analyzed at each DPOAE frequency in post series III evaluations and post VI series. Evaluation of DPOAE post series III at a frequency of 988 Hz as many as 10 ears (73.7%) with a decrease in the threshold of DPOAE threshold from baseline >4 dB indicating the possibility of an ototoxic state. At the DPOAE frequency of 1482 Hz, participants with a decrease in the DPOAE threshold from baseline >4 dB occurred in 8 ears. Evaluation at the frequency of 2222 Hz the difference in the decrease in the DPOAE threshold from baseline >4 dB occurred at 10 ears, and at a frequency of 2963 Hz the difference in the decrease in the DPOAE threshold from baseline >4 dB occurred in 16 ears. Evaluation at the frequency of 4444 Hz the difference in the decrease in the threshold of DPOAE from baseline >4 dB occurred at 17 ears, at a frequency of 5714 Hz the difference in the decrease in the threshold of DPOAE from baseline >4 dB occurred in 20 ears.

Evaluation of DPOAE at a frequency of 8000 Hz found that the difference in the decrease in the DPOAE threshold from baseline >4 dB occurred in 23 ears. In this study also carried out ototoxicity assessment at each frequency by calculating the difference in DPOAE values from the baseline pre-chemotherapy threshold with DPOAE series III and VI threshold values ranging from frequency 988 Hz to a frequency of 8000 Hz. Ototoxicity is expressed if there is a decrease in the threshold of >4 dB from the baseline. In this study (table 4) can be described the percentage of the most ears after series III which experienced a decrease in threshold >4 dB from baseline values ranging from 2963 Hz at 42.1%, frequency 4444 Hz at 17%, frequency 5714Hz at 20% and frequency 8000 Hz of 60.5%.

DPOAE evaluation after series VI chemotherapy was also analyzed at a frequency of 988 Hz, the difference in decrease in DPOAE threshold from baseline >4 dB occurred at 18 ears, at a frequency of 1482 Hz the difference in DPOAE threshold from baseline >4 dB occurred at 15 ears, and at a frequency of 1482 Hz occurs in 12 ears, at a frequency of 2222 Hz occurs in 12 ears. Evaluation of the frequency of 2953 Hz found that the difference in decreasing the DPOAE threshold from baseline >4 dB occurred at 25 ears, at a frequency of 4444 Hz occurring at 28 ears, evaluation at a frequency of 5714 Hz occurred at 29 ears and at 8000 Hz participants with a decrease in DPOAE threshold from baseline >4 dB occurs in 23 ears. The relationship between DPOAE results and pure tone audiometry was also analyzed for 38 ear samples (table 5) carried out in post series III evaluation with a sensitivity value of 0.50 (50%), a specificity value of 0.56 (56%), a positive predictive value of 0.18 and a value negative prediction of 0.86.

Table 5. Accuracy of DPOAE Evaluation Results with Series III Audiometry (n=38)

DPOAE 3	AUDIOMETRY 3			P
	Ototoxic	Normal	Total	
Ototoxic	3	14	17	0.778*
Normal	3	18	21	1.00**
Total	**6**	**32**	**38**	**0.778***

*Pearson Chi-square
**Continuity Correction
***Likelihood Ratio

In the post VI series evaluation (table 6) the sensitivity value was 0.64 (64%), and specificity was 0.69 (69%), the positive predictive value was 0.74, and the negative predictive value was 0.58.

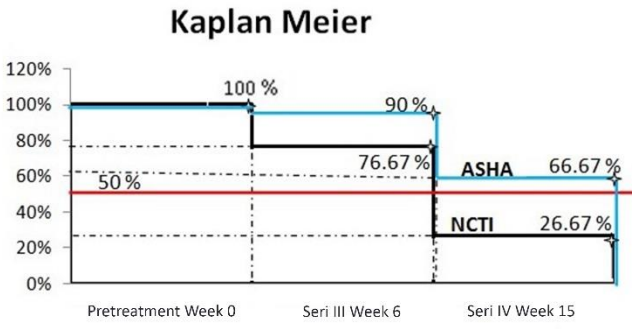
Table 6. Accuracy of DPOAE Evaluation Results with Series VI Audiometry (n=38)

DPOAE 3	AUDIOMETRY 6			P
	Ototoxic	Normal	Total	
Ototoxic	14	5	19	0.049*
Normal	8	11	19	0.1**
Total	**22**	**16**	**38**	**0.049***

*Pearson Chi-square
**Continuity Correction
***Likelihood Ratio

Based on Kaplan Meier survival analysis (graphic 2) the speed of ototoxicity was obtained in post-series III evaluation (6 weeks) of 23 participants with a survival rate of 76.67% and post-chemotherapy evaluation series VI (15 weeks), participants participated in 8 participants. with a percentage number of 26.67%. The ototoxic percentage at mid-cycle is 23.33% and at the end of the cycle reaches more than 50%, which is 73.33%.

Graphic 2. Kaplan Meier Analysis of the Speed of Occurrence of Ototoxicity Based on NCI-CTCAE Criteria (n=30)



Based on the ASHA criteria (graphic 2) audiometry evaluation after series III chemotherapy found the percentage of participants who experienced ototoxic only 10% and participants who still did not have ototoxic or normal as much as 90%. Evaluation after series VI found the percentage of participants who experienced ototoxic as much as 33.30%, and participants who were still in the normal category were 66.67%.

3.3 Analysis of bivariate of variables that are risk factors on decreasing hearing functions

Based on bivariate statistical analysis using the Spearman non-parametric correlation test, there was a significant relationship between the mean dose and the decrease in the hearing threshold. p=0.00 (<0.01). Kidney clearance (CCT) and decreased hearing threshold have a significant relationship p=0.00<0.01. Age of respondents with a decrease in hearing threshold did not have a significant relationship p=0.081 (>0.01). The mean dose correlation and decrease in hearing threshold is r=0.719 (>0.01), this indicates that there is a strong and positive relationship (not contradictory thus the higher the dose, the higher the risk of decreasing hearing water hearing threshold. Kidney and decreased hearing threshold are r=0.833 (>0.01) this indicates that there is a relationship.

4. DISCUSSION

The ototoxic incidence of carboplatin increases as the increase in drug accumulation occurs at around 33%. Parson et al9 found that 82% of patients experienced significant hearing loss after high-dose carboplatin chemotherapy. Schweitzer (1993) calculated the incidence of cisplatin, which induces mean hearing loss of about 62% (range between 11% -97%). According to Kennedy et al. 20 (1998), the incidence of carboplatin inducing hearing loss is estimated to be around 19% -83%. According to Blackley et al. (1994), the risk factors that cause hearing loss in the use of ototoxic drugs are generally associated with doses, although many other factors play a role. According to Fischel-Ghidsian45, the possibility of ototoxicity that causes hearing loss in each is influenced by various biochemical processes, physiological factors, and genetic factors. In this study, a bivariate correlation analysis was performed using the Spearman nonparametric correlation test, which found a significant relationship between the mean dose and the decrease in the hearing threshold. p=0.005 (<0.01). There was a significant correlation between mean dose and kidney clearance in creatinine clearance (CCT), i.e. p=0.005 (<0.01). Several studies have been conducted on the effect of the cumulative dose of carboplatin on ototoxicity and obtained a cumulative dose above 400 mg/m2. Li, Womer, and Sibler (2004) in their study conducted a pure tone audiometry assessment of 153 children, ages 5 to 18 years who received cisplatin therapy at therapeutic doses of 40 to 200 mg/m2 each cycle. The risk of bilateral hearing loss at high frequencies occurs significantly, along with the increase in the cumulative dose of the drug (p<0.005). Research conducted by Brock et al. (1991) 26 retrospectively assessed 29 children who had been treated with 60-100 mg/m2 each cycle [1-7, 20, 24].

The ototoxic risk increased significantly according to the cumulative dose of the drug (p=0.027). There has been no evidence of loss hearing in patients who received a therapeutic dose of <400 mg/m2 per cycle of chemotherapy. 19-21.26 The mean dose correlation and decrease in hearing threshold were r=0.719 (>0.01) indicating that there was a strong relationship and the direction of a positive relationship (not different thus the higher the total dose, the higher the decrease in hearing water hearing threshold. Lakhai (2006) 56 in his study concluded that the risk of hearing loss due to ototoxic drugs generally depends on the dose, duration, frequency and method of administration of the drug [35-37].

Age of respondents with a decrease in hearing threshold did not have a significant relationship p=0.101 (>0.01). Age of the respondent and kidney clearance, there was no significant relationship p = 0.079. Various studies have found an association between age and an increase in ototoxic events induced by platinum group chemotherapy [22, 28, 35].

The incidence increases especially in children and the elderly. Li et al. (2004) 56 examined pediatric patients with a mean age of less than 5 years who received carboplatin therapy. It was found that about 40% of children experience moderate to severe sensorineural hearing loss after receiving a cumulative dose of >400 mg/m2. The risk of only 5% occurs in children aged 15-20 years. Helson et al. (1978) have also investigated the ototoxic induced platinum group chemotherapy drugs with a cumulative dose of >400 mg/m2, and the incidence of sensorineural hearing loss was increased at the age of 46 years [7, 36-39].

Age correlation and decrease in hearing threshold r=-0.217 a weak correlation (negative) leads to a weak correlation. Correlation of age and kidney clearance r=-0,229 occurs weak correlation leads to negative (opposite). Correlation of mean doses and renal clearance: r = 0.816 (>0.01) this indicates that there are a very strong relationship and the direction of a positive relationship (not contradictory (support). The assessment of renal function is done by measuring creatinine clearance levels. Bokemeyer et al (1998) 41 examined the risk of ototoxicity in 86 patients who had complete remission of about 12 months [40-42].

Serum creatinine levels were measured after cisplatin administration and in patients who showed increased creatinine levels (92 μmol) experienced persistent sensorineural hearing loss symptoms compared with patients with lower creatinine levels (92 μmol) (p=0.04). Schaefer et al42 conducted a study on patients with impaired renal function (poor creatinine clearance) had a greater risk of ototoxic events as drug dosages increased. Correlation of renal clearance and decreased hearing threshold of water: r=0.833 (>0.01) this indicates that there is a powerful relationship, and the direction of a positive relationship ling supports. [43-45].

5. CONCLUSION

There was an effect of the administration of carboplatin chemotherapy regimen for 6 series chemotherapy (1 cycle) on hearing function in patients with head and neck regional carcinoma in the form of a significant decrease in bone delivery threshold and air delivery. The incidence of loss hearing in the administration of carboplatin chemotherapy is influenced by the average dose of the drug given and the individual clearance level of creatinine. DPOAE can be a good alternative screening tool in monitoring the ototoxicity of chemotherapy drugs.

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